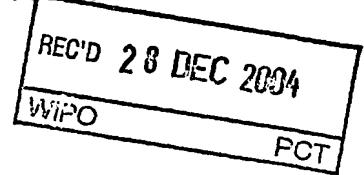




Europäisches
Patentamt

European
Patent Office

Office européen
des brevets



Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03078564.6

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

BEST AVAILABLE COPY



Anmeldung Nr:
Application no.: 03078564.6
Demande no:

Anmelde tag:
Date of filing: 17.11.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

DSM IP Assets B.V.
Het Overloon 1
6411 TE Heerlen
PAYS-BAS

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Process for the preparation of aliphatic primary alcohols and related
intermediates in such process

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State>Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07F7/00

Am Anmelde tag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

PE21709

- 1 -

PROCESS FOR THE PREPARATION OF ALIPHATIC PRIMARY ALCOHOLS AND
RELATED INTERMEDIATES IN SUCH PROCESS

High-molecular-weight aliphatic saturated primary alcohols, for instance with 20-40 C-atoms are useful products for use for instance in food or pharmaceutical products. For instance policosanol is a mixture of high-molecular-weight aliphatic primary alcohols with as its main component octacosanol (C28). It is used for instance for improvement of serum lipid profiles, which makes it an interesting compound for the prevention and treatment of cardiovascular diseases, and as a cholesterol-lowering additive in foods.

These alcohols, often mixtures thereof, are normally isolated from natural sources, for instance bees wax or plant sources such as sugar cane wax, rice bran wax and birch bark. A disadvantage of these processes is that the isolation is difficult and tedious, and therefore, expensive. Moreover it is difficult – if so desired – to obtain any given compound in pure form from the mixture. Also if a specific mixture of compounds is desired because this is advantageous for the biologic activity, such specific mixture is difficult to obtain.

A synthetic method therefore would be highly desirable. A number of synthetic methods are described in the literature. For instance in WO-A-02/059101 a synthetic route for the preparation of high-molecular-weight linear straight-chain primary alcohols starting from cyclotetradecanone is disclosed. After enamine formation with a cyclic secondary amine, a ring expansion is achieved by reaction with an activated alkanoic acid. The ring is opened in a further transformation and after two more steps the final alcohol is obtained. The synthesis is a 5-step sequence and moreover comprises a.o. a metal hydride reaction which is not attractive on commercial scale from a viewpoint of safety and costs.

In JP 61159591, an electrolytic Kolbe cross-coupling of two different long-chain carboxylic acids is described. An intrinsic element of such cross-coupling is that it leads to a mixture of products. It results in the formation of a 1-alkanoic acid methyl ester that is afterwards reduced to the 1-alkanol. Such processes, however, are commercially less attractive because they require specialized equipment, lead at best to moderate yields and require significant purification procedures.

The present invention now makes it possible to prepare high-molecular-weight aliphatic linear, straight-chain primary alcohols in a simple synthetic

- 2 -

process.

Of course, also specific mixtures of high molecular-weight aliphatic linear straight-chain primary alcohols can easily be prepared e.g. by the choice of the starting materials.

Key intermediates in such processes are protected primary alcohols

5 with formula (1)



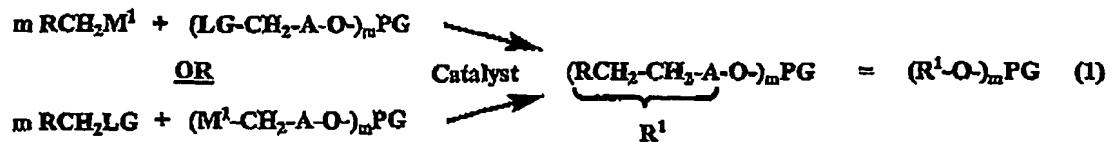
wherein R¹ represents a linear, straight-chain alkyl group having 26-30 C-atoms, m is 1
10 or 2 and PG represents a protecting group chosen from the group of (substituted) methyl ethers, for instance methoxymethyl, benzyloxymethyl, tetrahydropyranyl, 4-methoxytetrahydropyranyl, (substituted) ethyl ethers, for instance 1-ethoxyethyl, 1-methyl-1-benzyloxyethyl, 2-(benzylthio)ethyl, p-chlorophenyl, (substituted) benzyl ethers, for instance benzyl, 2,6-dichlorobenzyl, 2-picoly, triphenylmethyl and
15 (substituted) silyl ethers with sufficient stability under the reaction conditions under which they are formed and/or the work up thereof, of which at least one of the substituents on the Si-atoms is not a methyl group, for instance triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, t-butylmethoxyphenylsilyl, if m = 1; or a protecting group for dihydroxy functionalities (diol protecting group) if m = 2. The terms
20 (substituted) methyl ethers, (substituted) ethyl ethers, (substituted) benzyl ethers and (substituted) silyl ethers have the meanings as described by T.W. Greene & PGM. Wuts in Protecting Groups in Organic Synthesis, 3rd Edition, Wiley & Sons: New York, 1999, pp 17-19 and pp 27-148; protecting groups for compounds with dihydroxy functionality are for instance described on pp 201-241 of this same reference (Greene & Wuts).

Such compounds, and mixtures of such compounds, wherein R¹ represents a linear straight-chain alkyl group with 26-30 C-atoms and PG is as defined above are novel intermediates. The invention therefore also relates to such novel intermediates.

30 In one embodiment the key intermediates with formula (1) are prepared via a so-called organometallic cross-coupling reaction. Such organometallic cross-coupling reactions appeared to work very well, even in the presence of other functional groups.

One example of such an organometallic cross-coupling reaction is
35 schematically as given below.

- 3 -



R is H, C ₁₋₂₈	A is C ₀₋₂₈	$m = 1, 2$
------------------------------------	---------------------------------	------------

- 5 It represents the reaction of a straight-chain nucleophilic organometallic reagent of formula RCH_2M^1 with a linear, straight-chain electrophile of formula $(\text{LG}-\text{CH}_2-\text{A}-\text{O})_m\text{PG}$ (or a linear, straight-chain electrophile of formula RCH_2LG with a nucleophilic organometallic reagent of formula $(\text{M}^1-\text{CH}_2-\text{A}-\text{O})_m\text{PG}$), wherein $m = 1$ or 2 , R is H or a linear straight-chain alkyl group with 1-28 C-atoms, M^1 represents Li, 10 Na, K, BZ₂ (wherein Z=OH, an alkyl or alkoxy group, for instance an alkyl or alkoxy group with 1-10 C-atoms, or the 2 Z-groups together may form a 2-7 membered hydrocarbon ring with for instance 2-20 C-atoms, for instance 9-BBN), MgX (wherein X=halogen, for instance Cl, Br, I), ZnX (wherein X= halogen, for instance Cl, Br, I, or CH₂Si(CH₃)₃), MnX (wherein X=halogen, for instance Cl, Br, I), A is a C₀₋₂₈ linear, 15 straight-chain alkylene group, LG represents a leaving group (as, for instance, described in D.S. Kemp & F. Vellaccio, Organic Chemistry, Worth: New York, 1980; pp 99-102, 143-144, 179-180, for example F, Cl, Br, I, OSO₂Ar (Ar represents an aryl group), OMs (OMs represents a mesylate group), OTf (OTf represents a triflate group), OP(O)(OR¹¹)₂ (R¹¹ is an alkyl group, preferably an alkyl group with 1-5 C-atoms), PG is 20 as described above, to produce a linear straight-chain protected alcohol of formula (R¹-O)_mPG. The reaction preferably is carried out in the presence of a transition metal catalyst, which may be in the form of a neutral or cationic metal complex ML¹_aL²_bX, an anionic complex Q_d[ML¹_aL²_bX]_c⁻, a soluble transition metal nanocluster, or as heterogeneous catalyst wherein the metal in the zero oxidation state is deposited in the 25 form of microcrystalline material on a solid carrier, wherein M can be any transition metal known to catalyze such coupling reactions, for instance Mn, Fe, Cu, Ni or Pd. L¹ and L² are ligands (for instance optionally substituted phosphines and bisphosphines such as triphenylphosphine, bis-diphenylphosphinopropane, 1,1'-diphosphaferrrocene (dppf), phosphites or bisphosphites, PN ligands in which there is both a coordinating P atom and a N atom present, N-N ligands such as phenanthrolines), X is an anion which 30 may be a halide, a carboxylate or a composite anion such as BF₄⁻ or PF₆⁻, Q is a cation

for instance an alkaline metal ion (for instance sodium, potassium) or a tetraalkylammonium salt, a, b, c, d and e are integers from 0-5. The clusters contain from 2 to many thousands of metal atoms and may carry ligands or anions on the outer rim. Suitable carrier materials for heterogenous catalysts are, for instance, carbon black, silica, aluminum oxide. Particularly when M¹ represents an alkali metal, e.g. Li, Na or K, a metal catalyst is not particularly preferred. Both R and A are saturated (contain no double bonds). In the product of formula (1), R¹ (is RCH₂-CH₂A) is a C₂₈₋₃₀ linear, straight-chain alkyl group and PG is as above. The reaction preferably is performed under an inert atmosphere (e.g. dry nitrogen or dry argon).

In a preferred embodiment of this organometallic coupling, an alkyl magnesium halide, most preferably an alkyl magnesium chloride or bromide (for instance an amount of 1 to 5 equivalents, preferably 1-2 equivalents) is reacted with 1 equivalent of an alkyl halide or alkyl arylsulfonate, alkyl mesylate or alkyl triflate, most preferably with an alkyl fluoride, alkyl chloride, alkyl bromide, alkyl mesylate or alkyl tosylate in the presence of a transition metal catalyst; as for instance described in Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* 2002, 124, 4222-4223, and Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* 2003, 125, 5646-5647. Preferably the reaction is carried out in the presence of a solvent. Suitable solvents are for instance ethyl ether, tetrahydrofuran (THF), *i*-propyl ether di-*n*-propyl ether, dimethoxyethane (DME) or methyl *t*-butyl ether or mixtures of these solvents with a dipolar aprotic solvent such as NMP, DMF or DMA (dimethylacetamide) in any proportion, most preferably THF, and the concentration of each of the reactants is preferably between 0.2 and 3 molar. The transition metal catalyst is based on a transition metal M chosen preferably from Mn, Fe, Cu, Ni, Pd. They can be in the form of pre-formed complexes or made *in situ* from a catalyst precursor and one or more ligands. If desired an activator (for instance a base, such as an alkoxide, or a reducing agent, such as NaBH₄) may be added to these complexes. Suitable sources of catalyst precursors are for instance precursors of Cu^I (for example CuCl, CuI, CuOTf), Cu^{II} (for example CuCl₂, Li₂CuCl₄), Ni⁰ (for example Ni(COD)₂), Ni^{II} (for example NiCl₂, Ni(acac)₂, NiBr₂), or Pd^{II} (for example PdCl₂, Pd(OAc)₂, Pd₂(dba)₃), Mn^{III} (for example MnCl₃, Mn(acac)₃) or Fe^{III} (for example Fe(acac)₃). Preformed catalysts can also be used, for example (PPh₃)₂NiCl₂, (dppp)NiCl₂ or (dppt)NiCl₂. The amount of catalyst that is used is calculated with respect to the electrophile and is preferably lower than 0.05 equivalents, more preferably between 0.001 and 0.03 equivalents calculated with respect to the electrophile. Preferably less than 4

equivalents of each ligand with respect to the amount of metal M are used. Optionally, the reaction is run in the presence of a 1,3-diene, for example 1,3-butadiene, isoprene or 2,3-dimethyl-1,3-butadiene, in a relative amount of 0.1 to 2.0 equivalents calculated with respect to the electrophile. The temperature at which the reaction is performed

5 preferably lies between -78 to 80 °C, more preferably between -20 and 80 °C. The reaction time required is preferably between 1 and 24 hours.

In a second preferred embodiment, the nucleophilic reagent may be of the general structure RCH_2ZnX (wherein for example X=Br,I or CH_2SiMe_3 , and R is as above); as for instance described in Jensen, A. E.; Knochel, P. J. Org. Chem. 2002, 10 67, 79-85. Preferably, an alkylzinc iodide (preferred amount 1.05-1.5 equivalents calculated with respect to the electrophile) is reacted with 1 equivalent of an alkyl bromide or iodide, preferably iodide, optionally in the presence of a tetraalkylammonium halide R^3NX , wherein each R^3 , independently, represents an alkyl group, for instance an alkyl group with 1-16 C-atoms and X represents a halogen, for 15 instance Cl, Br or I, for instance $n\text{-Pr}_4\text{NI}$, $n\text{-Bu}_4\text{NBr}$, $n\text{-Bu}_4\text{NI}$ (preferred amount 1-5 equivalents with respect to the alkyl halide), and optionally in the presence of a styrene preferably a mono- or polyfluorinated styrene, such as *m*-fluorostyrene or *p*-fluorostyrene (preferred amount 0.05-0.30 equivalents calculated with respect to the electrophile) and a Ni^{II} catalyst, such as NiCl_2 , $\text{Ni}(\text{acac})_2$, NiBr_2 , $(\text{PPh}_3)_2\text{NiCl}_2$, 20 $(\text{dppp})\text{NiCl}_2$, in a relative amount between 0.01 and 0.20 equivalents calculated with respect to the electrophile. The reaction preferably is carried out in the presence of a solvent. Suitable solvents that may be used are for instance ethers, NMP, DMF or mixtures thereof. The reaction preferably is run at temperatures between -30 and 25 °C. The reaction time required preferably is between 2 and 30 h.

25 In a third preferred embodiment, the nucleophilic reagent may be of the general structure $\text{RCH}_2\text{BR}^4_2$ (wherein each R^4 independently represents an alkyl group, for instance an alkyl group with 1-10 C-atoms, or may be part of a ring, for instance as in 9-BBN), $\text{RCH}_2\text{B}(\text{OH})_2$ or $\text{RCH}_2\text{B}(\text{OR}^4)_2$, wherein R is as above, as for instance described in Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. J. Am. Chem. 30 Soc. 2001, 123, 10099-10100, Kirchhoff, J. H.; Dai, C.; Fu, G. C. Angew. Chem. Int. Ed. 2002, 41, 1945-1947, Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. J. Am. Chem. Soc. 2002, 124, 13662-13663, and Netherton, M. R.; Fu, G. C. Angew. Chem. Int. Ed. 2002, 41, 3910-3912.

35 In one embodiment an alkyl-(9-BBN) reagent (preferred amount 1-3 equivalents, calculated with respect to the amount of electrophile), is reacted with for

instance an alkyl chloride, bromide or tosylate, preferably a bromide or a tosylate. The reaction is catalyzed by a source of Pd⁰ or Pd^{II}, such as Pd(OAc)₂, PdCl₂, or Pd₂(dba)₃, preferably Pd(OAc)₂, in an amount calculated with respect to the electrophile of 0.01-0.10 equivalents. Addition of a stabilizing ligand for the metal may be beneficial.

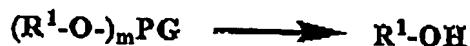
- 5 Suitable examples of such stabilizing ligands are PR⁵₃ (wherein each R⁵ independently represents a, for instance C1-C20, alkyl, aryl, heteroaryl, etc. group, e.g. P(i-Pr)₃, P(t-Bu)₃, PCy₃ (Cy=cyclohexyl), PPh₃, P(2-furyl)₃, P(t-Bu)₂Me), preferably PCy₃. The source of the phosphine ligand may also be the corresponding phosphonium salt (less susceptible to oxidation), such as (HP(t-Bu)₂Me)BF₄. The relative amount of the
- 10 phosphine may be 0.05-0.20 equivalents calculated with respect to the electrophile, preferably in a molar ratio 2:1 to Pd. In addition, as a rule a base is added, for instance a phosphate salt such as Na₃PO₄·H₂O or K₃PO₄·H₂O; an alkali metal hydroxide, for instance NaOH, KOH, LiOH or CsOH; or a bulky alkoxide base such as LiOt-Bu, NaOt-Bu or KOt-Bu, in a proportion of 1-4 equivalents calculated with respect to the
- 15 electrophile. The reaction preferably is carried out in the presence of a solvent. Suitable solvents that can be used are the ethers mentioned above, also dioxane or a bulky alcohol, such as t-amyl alcohol. THF is preferably used as the solvent with alkyl-(9-BBN) derivatives and t-amyl alcohol with alkyl boronic acids. In some cases, the addition of one or two equivalents of water with respect to the electrophile may be
- 20 beneficial. The reaction preferably is run at temperatures between 25 and 100°C (higher temperatures are preferred for more unreactive alkyl chloride electrophiles).

- In another embodiment, the nucleophilic reagent may be of the general structure RCH₂M¹ with M¹ = Li, Na, K and R is as above. It is reacted preferably with an alkyl halide or tosylate, preferably an alkyl bromide, iodide or tosylate. A metal catalyst is not particularly preferred in these cases. The stoichiometries of these reactions are as above (for instance an excess organometallic reagent, preferably 1-3 equivalents, most preferably 1-1.5 equivalents). The preferred solvents are here the ethers mentioned above (preferably THF), but also toluene can be suitably used, especially when higher reaction temperatures are required.

- 30 Subsequently the protected alcohols with formula (1) and mixtures thereof can be converted into the desired, corresponding unprotected alcohols with formula R¹OH and mixtures thereof wherein R¹ is as defined above.

- 35 Processes for deprotection are commonly known in the art. The skilled person can easily find a suitable method for their case. Some examples are given below.

- 7 -

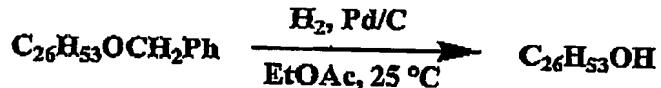


For example:



An example of a removal of a common PG from a protected higher (C28) alkanol is shown above. The PG methoxymethyl ether can for instance be cleaved under acidic conditions in methanol, at reflux.

10 Another PG, for example, a benzyl group, can be removed under reductive conditions, in the presence of hydrogen gas and a palladium catalyst:



In yet another example, where the PG is a *t*-butyldimethylsilyl group, deprotection can be easily achieved, for instance, by fluoride ion in THF at 25 °C, 15 originating from, for example, tetrabutylammonium fluoride:



For further details about the above and other protecting groups, see T. W. Greene & P. G. M. Wuts in Protecting Groups in Organic Synthesis, 3rd Edition, Wiley & Sons: New York, 1999; pp 27-148.

CLAIMS

1 Protected alcohol with formula (1)

$$5 \quad (\text{R}^1 - \text{O}-)_m \text{PG} \quad (1)$$

wherein R¹ represents a linear, straight-chain alkyl group having 26-30 C-atoms, m is 1 or 2, and PG represents a protecting group chosen from the group of (substituted) methyl ethers, (substituted) ethyl ethers, (substituted) benzyl ethers and (substituted) silyl ethers with at least one substituent on the Si-atom being not a methyl group, in case m = 1; and a diol protecting group in case m = 2.

1. Process for the preparation of a protected alcohol according to claim 1 via an organometallic cross coupling reaction wherein a linear, straight-chain nucleophilic organometallic reagent of formula RCH_2M^1 is reacted with a linear, straight-chain electrophile of formula $(LG-CH_2-A-O-)_mPG$ (or a linear, straight-chain electrophile of formula RCH_2-LG with a nucleophilic organometallic reagent of formula $(M^1CH_2-A-O-)_mPG$), wherein $m = 1$ or 2 ,

15 R is H or a linear, straight-chain alkyl group with 1-28 C-atoms,
 M^1 represents Li, Na, K, BZ₂, wherein each Z independently represents OH, an alkyl group or an alkoxy group, or the 2 Z-groups together form a hydrocarbon ring, MgX, wherein X=halogen, ZnX, wherein X= halogen or CH₂Si(CH₃)₂, or MnX, wherein X=halogen,

20 A is a C₀₋₂₈ linear, straight-chain alkylene group,

25 LG represents a leaving group.

PG is as described in claim 1.

3. Process according to claim 2, wherein the organometallic cross coupling reaction is performed in the presence of a transition metal catalyst and wherein M^1 represents MgX with X is halogen.

30 4. Process according to claim 3, wherein the nucleophilic organometallic reagent reacts with an alkyl halide, alkyl arylsulfonate or alkyl mesylate.

5. Process according to any one of claims 2-4, wherein first the protected alcohol with formula (1) is prepared according to any one of claims 2-4 and subsequently the protected alcohol is subjected to deprotection.

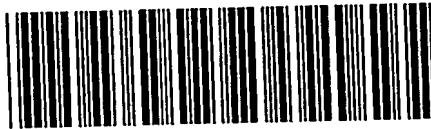
35

- 9 -

ABSTRACT

- The invention relates to protected alcohol with formula $(R^1 - O -)_m PG$,
wherein R^1 represents a linear, straight-chain alkyl group having 26-30 C-atoms, m is 1
5 or 2, and PG represents a protecting group chosen from the group of (substituted)
methyl ethers, (substituted) ethyl ethers, (substituted) benzyl ethers and (substituted)
silyl ethers with at least one substituent on the Si-atom being not a methyl group, in
case m = 1; and a diol protecting group in case m = 2.
- 10 The invention further relates to process for the preparation of such
protected alcohols via an organometallic cross coupling reaction.

PCT/EP2004/013160



**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.